

IFN-gamma and TNF-alpha Synergistically Induce Mesenchymal Stem Cell Impairment and Tumorigenesis via NFkappaB Signaling.

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Public Summary:

Mesenchymal stem cells (MSCs) are non-hematopoietic multipotent stem cells capable of differentiating into both mesenchymal and non-mesenchymal cell types. In addition to offer cell-based tissue regeneration and immune therapies, MSC deficiency may contribute to a variety of human diseases, such as osteoporosis and cancers. However, the detailed mechanism in which MSCs involve in physiopathology of human diseases is not fully understood. In this study, we identified that proinflammatory cytokines interferon γ (IFN- γ) and tumor necrosis factor α (TNF- α) together, but not independently, cause MSC deficiency via NFkB-mediated activation of smad7, whereas long-term elevated levels of IFN- γ and TNF- α synergistically result in increased tendency toward MSC malignant transformation through NFkB-mediated upregulation of the oncogenes c-fos and c-myc. Blockage of either IFN- γ or TNF- α abolishes MSC impairment and the tendency toward malignant transformation. To translate our finding to potential clinical therapies, we showed that systemic administration of Aspirin, which significantly reduces the levels of IFN- γ and TNF- α , resulted in blockage of MSC deficiency and tumorigenesis. Taken together, this study reveals that IFN- γ and TNF- α , critical inflammatory factors, synergistically induce impairments of MSCs via NFkB/smad7 signaling and MSC tumorigenesis by activating NFkB-mediated oncogene activation. The significance of this study is to identify a novel role of combinative effect of inflammatory factor (IFN- γ and TNF- α) in inducing stem cell deficiency (osteoporosis) and tumorigenesis (osteosarcoma). Based on this finding, a practical anti-inflammation treatment, such as using Aspirin, was developed to improve MSC function and prevent MSC-associated tumorigenesis. This study may also provide experimental evidences to explain the reason that long-term Aspirin use may prevent tumorigenesis.

Scientific Abstract:

An inflammatory microenvironment may cause organ degenerative diseases and malignant tumors. However, the precise mechanisms of inflammation-induced diseases are not fully understood. Here, we show that the proinflammatory cytokines interferon-gamma (IFN-gamma) and tumor necrosis factor alpha (TNF-alpha) synergistically impair self-renewal and differentiation of mesenchymal stem cells (MSCs) via nuclear factor kappaB (NFkappaB)-mediated activation of mothers against decapentaplegic homolog 7 (SMAD7) in ovariectomized (OVX) mice. More interestingly, a long-term elevated levels of IFN-gamma and TNF-alpha result in significantly increased susceptibility to malignant transformation in MSCs through NFkappaB-mediated upregulation of the oncogenes c-Fos and c-Myc. Depletion of either IFN-gamma or TNF-alpha in OVX mice abolishes MSC impairment and the tendency toward malignant transformation with no NFkappaB-mediated oncogene activation. Systemic administration of aspirin, which significantly reduces the levels of IFN-gamma and TNF-alpha, results in blockage of MSC deficiency and tumorigenesis by inhibition of NFkappaB/SMAD7 and NFkappaB/c-FOS and c-MYC pathways in OVX mice. In summary, this study reveals that inflammation factors, such as IFN-gamma and TNF-alpha, synergistically induce MSC deficiency via NFkappaB/SMAD7 signaling and tumorigenesis via NFkappaB-mediated oncogene activation. *STEM Cells* 2013;31:1383-1395.

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